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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,032	09/24/1999	WILLIAM J. BOYLE	A-378-CIP2C4	9035

21069 7590 04/20/2004

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/405,032	BOYLE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-67 and 69-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-67 and 69-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 12/10/03 has been entered. Claims 61 and 69 have been amended. Claims 61-67 and 69-76 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in 12/10/03 response would be addressed to the extent that they apply to current rejection.

Specification

The specification is objected because the *status* of the previous U.S. applications to which this application claims priority has not been updated for each of the applications in the continuation chain recited in the first paragraph of the specification.

The specification is objected because the amendments to the claims do not comply with the Revised Amendment Practice of 37 CFR 1.121 (See OG Notice 23 September 2003). Specifically, the text of canceled claim (68) must be omitted.

Appropriate correction is required.

Claim Objections

Claim 61 is objected to because of the following informalities: the deleted text has not been properly marked. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-67 and 69-76 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and the arguments in the remarks would be addressed in the order that they appeared in the Remarks.

Applicants first argue that they have provided a Declaration of Dr. Sheng and a publication of Bolon et al (2001) as evidence of enablement, and that the ovarectomized mouse is a clinical relevant model for loss of bone mass (Remark, page 7, 3rd paragraph).

In response, as indicated in page 6 of paper #17, since the original disclosure is silent regarding the instantly claimed subject matter, a later filed declaration and publication could not supplement the essential element that is missing from the specification. As stated in In re Glass, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The fact that the specific protocol is not disclosed in the specification indicates that the specification does

not support the claims as filed, but instead reflects further critical information that is essential for the artisan to practice the invention.

Applicants go on to argue that the specification itself describes and enables the claimed invention pointing to page 20, lines 22-24, and page 33, lines 20-27. Applicants also argue, citing *Genentech Inc. v. Novo Nordisk* A/S, 42 USPQ2d 1005 (CAFC 1997) as support, that only the novel aspects of the invention is needed in the disclosure, which is, in this case, the identification and characterization of OPG and its biological activity.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

The indicated sentence and paragraph of the specification briefly contemplates that the nucleic acids of the invention is useful for either antisense or gene therapy, which is only a vague concept of utility for the nucleic acid, which awaits significant development to its practical level. Whereas given the broadest reasonable interpretation, the claims are directed to a therapeutic method for treating bone loss in a mammal comprising administering to the mammal *any* expression vector expressing *any* OPG with/*without* the ligand-binding and Fc region via *any* route of administration, whereby a therapeutic benefit should be obtained. The specification as originally filed fails to disclose administering a nucleic acid in the ovarectomized mouse model, it fails to disclose an adenoviral vector and intravenous injection as appropriate means for the nucleic acid delivery, and it fails to teach other type of vector nor routes of administration for a nucleic acid composition. Hence, the specification as originally filed

fails to disclose the essential elements that lead to the enablement of the claimed method.

With respect to the novel aspects of the invention, although the identification and characterization of OPG and its biological activity is essential for practice the invention, the identified OPG by itself is insufficient for practice the instantly claimed invention in view of the state of the art at the time the effective filing date. The Office has cited numerous art of record such as *Robbins et al, Orkin et al, Bolon et al, Crystal et al, Miller et al, Deonarain et al, Baylink et al, and Anderson* to establish that at the time of the invention, the art of gene therapy is still undeveloped, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. As indicated by *French Anderson,* who (Hum Gene Ther 2002;13:1261-2) compared the reality in practicing gene therapy with the launching of space shuttle. "THERE ARE HUNDREDS OF CRITICAL STEPS, ALL OF WHICH MUST WORK SMOOTHLY AND EFFICIENTLY FOR THE WHOLE MISSION TO BE SUCCESSFUL...EVERY SYSTEM MUST BE HIGHLY SOPHISTICATED IN ORDER TO ENSURE SUCCESS. SO, TOO, WITH THE GENE THERAPY" (Section 1, page 1261), who asked at the time long after instant filing date, "WHY HAS IT BEEN SO HARD TO OBTAIN SUCCESS IN GENE THERAPY CLINICAL TRIALS", and who predicted that 2005 may see the first licensed gene therapy product. These teachings establish that the nature of the transgene, the vector construct used, the means of delivery, and models and criterias for evaluation are all contributing to the novel aspects of gene therapy, and these elements were not yet routine for gene therapy at the time of instant filing date.

Accordingly, the following case law still applicable to the instant case wherein the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required;** there is a **failure** to meet the enablement requirement that **cannot** be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Therefore, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was *neither routine nor accepted*, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. However, the specification fails to provide any guidance regarding the essential elements needed for practicing the instantly claimed invention. Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* OPG gene expression at therapeutic levels, in particular for the treatment of any and all diseases associated with bone loss, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to the breadth of the claims directed to any OPG, any expression vector and any

route of administration, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants further argue that the scope of the claimed subject matter does not require undue experimentation, that OPG is still present in animals receiving single does of Ad-hOPG or Ad-mOPG even after 25 days as reported in Bolon publication, that routine changes such as increasing amounts of vector or frequency of administration would give therapeutic effect, and such changes would not require undue experimentation (Remark, paragraph bridging pages 8 & 9).

The arguments have been fully considered but they are not persuasive for reasons of record and because as taught by numerous cited references particularly *Robbins et al*, the cytotoxicity and immunogenicity of adenoviral vector has prevented the feasibility of repeated and higher dosing, thus, has been hampering the success of clinical gene therapy procedure, and such hurdle has not been overcome in general at the post-filing date. Accordingly, Applicants' assertion of routineness has not been proven true either by the specification or by the teachings of the skilled artisan.

Applicants go on to argue (2nd paragraph, page 9) that the Examiner has not pointed to any evidence that would suggest that the broadly claimed vectors would not be useful in expressing OPG and reducing bone loss. In response, applicants' attention is directed to pages 7 and 8 of the Office action paper # 17, wherein the limitations of each of the numerous vectors are cited as they were taught in *Robbins et al*. These limitations illustrated the general state of art with regard to the efficacy of gene delivery vehicles, which needs further development to the practical level. The enablement of

vectors has to be evaluated on a case-by-case basis as concluded by *Crystal et al* and *Miller et al*. Again, these teachings establish that it is not routine to use any vector known in the art to successfully delivering a therapeutic gene of interest to a subject in need, and obtaining therapeutic effect as now claimed. Applicants are reminded that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Applicants then argue that the statement of Bolon reference with respect of searching for more suitable vector is in no way prejudicial to the results they have already obtained (Remark, 3rd paragraph, page 9).

In response, the statement was cited to illustrate that the state of the art is still under development long after the effective filing date for a single type of vector encompassed by the claims, and hence when evaluating the state of the prior art as a whole, it is apparent that the specification has not provided sufficient support for the full scope of the invention, where there is no mention of the particular vector. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, for reasons of record and those set forth foregoing, the specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. § 112.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 61, 65-67, 69, and 73-76 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 11, and 12 of U.S. Patent No. 6,284,740 for reasons of record.

Applicants request that the rejection be held in abeyance pending an indication by the Examiner of allowable subject matter. Until then, the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Deborah Reynolds** can be reached on 571-272-0734. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.

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PATENT EXAMINER

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QJL
April 16, 2004